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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,619	03/30/2004	Po-Ying Chan-Hui	131.02US	3231

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EXAMINER	
HALVORSON, MARK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/812,619	CHAN-HUI ET AL.	
	Examiner	Art Unit	
	Mark Halvorson	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *2-8 and 13-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 9-12, 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/23/2004; 8/30/20*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group III, claims 1, 9-12, 21-26, is acknowledged and has been entered. Claims 1-26 are pending in the application and Claims 2-8 and 13-20 has been withdrawn from further consideration by the examiner under 37 C.F.R. 1.142(b) as being drawn to non-elected inventions. Claims 1, 9-12, 21-26 are currently under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 10 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining disease status of a patient suffering from prostate cancer comprising measuring the amount of VEGFR expression, does not reasonably provide enablement for method of determining disease status of a patient suffering from a disease characterized by aberrant expression of VEGFR2 comprising measuring VEGFR2 homodimers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to a method of determining disease status of a patient characterized by aberrant expression of a cell surface receptor complex wherein the receptor complex is VEGFR2 homodimers.

The specification describes disease status as the likelihood of contracting a disease, presence or absence of a disease, prognosis of disease severity and likelihood that a patient will respond to treatment by a particular therapeutic agent that acts through a receptor complex.

The specification includes VEGFR2 homodimers in the definition of VEGF receptor (page 15 lines 10-22) and list the VEGFR2 homodimes as one of 33 exemplary receptor complexes (see Table I).

Klagsbrun et al (US Patent No: 6,635,421) disclose a method for determining prognosis for prostate cancer in an individual comprising obtaining a tumor sample form the patient, measuring VEGF receptor amounts, correlating the receptor level with a baseline level wherein the baseline levels is determined by measuring VEGFR in a

sample of disease free individuals and correlating levels of receptor greater than the baseline with an indication of unfavorable prognosis (see column 5, lines 22-39; also column 10, lines 14-20).

Huss et al, (Cancer Res 61:2736-2743, 2001) describe VEGFR2 protein expression on high grade tumors but not in prostatic epithelial neoplasia or in well-differentiated or moderately differentiated lesions (see page 2741, column 1 1st paragraph to column 2 1st paragraph,). Thus VEGFR2 receptor expression was correlated with the transition from a differentiated to a poorly differentiated disease in a mouse prostrate cancer model (Id). There was no discussion concerning VEGFR2 homodimer expression.

In addition, Huang et al (Int J Biochem Cell Bio 33:315-324, 2001) disclose that the binding of VEGF-A to VEGFR2 results in the homodimerization of VEGFR2 (see page 316, 1st column, 2nd paragraph,). Huang et al further disclose that signal transduction through VEGFR2 homodimers in transfected cell lines is distinct from VEGFR1 homodimers and VEGFR1 and VEGFR2 heterodimers (see Abstract).

The art does not describe any correlation between the presence of VEGFR2 homdimers and the disease status of a patient. Furthermore, the specification of the present invention is silent on the correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient. There are no examples in the specification concerning the correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient.

Thus, given the vast number of potential diseases contemplated in the specification and the lack of any correlation between the presence of VEGFR homodimers in a patient sample and the disease status of the patient for any disease one could not predictably identify which disease would correlate with the presence of VEGFR2 homodimers with a reasonably expectation of success.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be reasonably predicted that a method for predicting the status of a disease correlates with the presence of VEGFR homodimers. Therefore, in view of the lack of predictability of the prior art, the breadth of the claims, the lack of guidance and support in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as broadly claimed.

3. Claims 12, 21-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 12 and 21-26 are drawn to a method for determining disease status of a patient utilizing a genus of **cleavage probes** and a genus of **binding compounds**.

The specification describes a binding compound as an antibody, a peptide or non-peptide ligand for a cell surface receptor, a protein, an oligonucleotide analog, such

as a peptide nucleic acid, a lectin or any other molecular entity capable of specific binding or stable complex formation with an analyte of interest (page 30 lines 32-36).

The specification states that a cleavage probe may comprise a primary haptenated antibody and a secondary anti-hapten binding protein derivatized with multiple photosensitizer molecules (page 39, lines 18- 19). The preferred anti-hapten binding protein may be either an anti-biotin antibody or streptavidin (page 39, lines 19-21). The specification describes a streptavidin-derived cleavage probe (page 43 line 7, page 46, line 31)

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

The Federal Circuit has recently clarified that a molecule can be adequately described without disclosing its complete structure. See Enzo Biochem, Inc. V. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying

characteristics ....i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. " Id. At 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus, the instant specification may provide an adequate written description of cleaving probes and binding compounds, per Lilly by structurally describing a representative number of cleaving probes and binding compounds that function as claimed or by describing structural features common to the members of the genus, which features constitute a substantial portion of the genus. Alternatively, per Enzo, the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

In this case, the specification does not describe the genus of binding compounds or the genus of cleaving probes in a manner that satisfies either the Lilly or Enzo standards. There are insufficient structural features common to all members of the genus of binding compounds and the genus of cleaving probes. The genus of binding compounds encompasses any molecular entity capable of specific binding or stable complex formation with an analyte of interest (page 30, lines 35-36). This encompasses proteins, nucleic acids and carbohydrates (page 30, lines 34-35). There is virtually no structural similarity between the genus of binding compounds as defined in the specification. The only binding compounds specifically described in the specification

are antibodies. One species of binding probes, antibodies, does not sufficiently describe the genus of binding probes and the claimed binding compounds do not meet the standard set forth in Lilly.

In addition does not describe the genus of cleaving probes in a manner that satisfies the Lilly standard. The cleaving probe is interpreted as being a binding probe directly or indirectly attached to a cleavage-inducing moiety. As described above the specification discloses only one species of binding probe. Furthermore, the specification only describes one species of cleavage-inducing moiety, a photosensitizer cleavage-inducing moiety. Thus, out of the whole genus of binding probes and genus of cleavage-inducing moieties the specification describes only one species of each. Thus the claimed peptides do not meet the standard set forth in Lilly.

The instant specification may also provide an adequate written description of the genus of binding compounds or the genus of cleaving probes if the specification can show that the claimed invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. The specification discloses only one species of binding compounds and one species of cleaving probes. Thus, the specification does not describe sufficient structural characteristics that correlate with the ability of the genus of binding compounds or the genus of cleaving probes to function as contemplated by the specification and for the reasons set forth above do not meet the standards set forth by Enzo.

Thus, the specification does not provide an adequate written description of the genus of genus of binding compounds or the genus of cleaving probes of claims 12, 21-26 that is required to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e).

4. Claims 1, 9, and 11 are rejected under 35 U.S.C. 102(e) as being anticipated by Klagsbrun et al (US Patent No. 6,635,421, filed May 30, 2000).

The claims are drawn to a method of determining disease status of a patient comprising the steps of measuring directly in a patient sample an amount of eon or

more cell surface receptor complexes, comparing each such amount to its corresponding amount in a reference sample, and correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient, wherein the cell surface receptor is a VEGF receptor complex, wherein the disease is cancer.

Klagsbrun et al discloses a method for determining prognosis for prostate cancer in an individual comprising obtaining a tumor ample form the patient, measuring VEGF receptor amounts, correlating the receptor level with a baseline level wherein the baseline levels is determined by measuring VEGFR in a sample of disease free individuals and correlating levels of receptor greater than the baseline with an indication of unfavorable prognosis (see column 5, lines 22-39; also column 10, lines 14-20).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1, 9, 11, 12, 21-24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klagsbrun et al (US Patent No. 6,635,421, filed May 30, 2000) in view of Singh et al (US Patent No: 6,627,400, issued 9/30/2003, filed 10/27/2000).

The claims are drawn to a method of determining disease status of a patient comprising the steps of measuring directly in a patient sample an amount of one or more cell surface receptor complexes, comparing each such amount to its corresponding amount in a reference sample, and correlating differences in the amounts from the patient sample and the respective corresponding amounts from the reference sample to the disease status of the patient, wherein the cell surface receptor complexes are determined by utilizing a cleaving probe and a binding compound with a molecular tag attached by a cleavable linkage, wherein the cell surface receptors are mixed with the cleavage probe, the binding compound, and a tissue indicator such that the cleaving probe and the binding probe specifically bind to their respective targets and the cleavable linkages of the binding compound are with the effective proximity of the cleavage-inducing moiety so that molecular tags are released whereupon the molecular tags are released, whereupon the molecular tags are separated and identified to

determine the presence or absence of the cell receptor complex in the patient sample by identifying the released molecular tags, wherein the disease status is responsive to treatment with a dimer-acting drug, wherein the patient sample is a fixed tissue sample, wherein the tissue indicator is tubulin. VEGFR1 and VEGFR2 form homodimers and heterodimers (see specification, page 15. lines 17-22)

Klagsbrun et al discloses a method for determining prognosis for prostate cancer in an individual comprising obtaining a tumor sample from the patient, measuring VEGF receptor amounts on a fixed tissue sample , correlating the receptor level with a baseline level wherein the baseline levels is determined by measuring VEGFR in a sample of disease free individuals and correlating levels of receptor greater than the baseline with an indication of unfavorable prognosis (see column 5, lines 22-39; also column 10, lines 14-27; also column 11 lines 53-54). For claim 24 the search for a species of cancer was expanded to include prostate cancer.

Klagsbrun et al do not specifically teach cell surface receptor complexes are determined by utilizing a cleaving probe and a binding compound with a molecular tag attached by a cleavable linkage, wherein the cell surface receptors are mixed with the cleavage probe, the binding compound, and a tissue indicator such that the cleaving probe and the binding probe specifically bind to their respective targets and the cleavable linkages of the binding compound are with the effective proximity of the cleavage-inducing moiety so that molecular tags are released whereupon the molecular tags are released, whereupon the molecular tags are separated and identified to determine the presence or absence of the cell receptor complex in the patient sample.

Singh et al teaches a method for determining populations of surface membrane proteins in a cell sample comprising mixing the membrane proteins with binding compounds having releasable eTag reporters, and binding compounds conjugated with an active species producing moiety, whereupon the active species causes the cleavage of the eTag reporters when the binding compounds having releasable eTag reporters is complexed with the conjugated binding compounds and the surface membrane protein, whereupon the eTag reporters are released by the active species whereupon the eTags are separated and identified resulting in the determination of the population of surface membrane proteins in a cell sample (see claim 12).

While Klagsbrun et al do not explicitly disclose the tissue indicator, tubulin, this protein is a commonly used housekeeping protein expressed in almost every tissue sample and thus the tissue sample disclosed by Klagsbrun et al would inherently express the tissue indicator, tubulin.

One of ordinary skill in the art would have been motivated to apply Singh et al's method of determining the population of surface membrane proteins to Klagsbrun et al's method of determining the disease status of a patient by correlating differences in expression of a cell surface receptor because Singh et al describe a powerful tool for detecting surface membrane proteins and determine changes in the surface protein population due to neoplasia (see column 86 lines 27-34). It would have been prima facie obvious to one skilled in the art to use Klagsbrun et al method of determining the disease status of a patient by measuring the population of a cell surface receptor with Singh et al's method of determining the population of surface membrane proteins.

Summary

8. No claims allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Halvorson, PhD whose telephone number is (571) 272-6539. The examiner can normally be reached on Monday through Friday from 8:30am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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